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Impact of Red and Violet Laser Therapy on Peripheral Arterial Disease: Case Series

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Peripheral arterial diseases, Red and violet Laser therapy, Surgery.

Introduction
Peripheral arterial disease (PAD) is a manifestation of atherosclerotic disease impacting the lower section of the aorta, along with its primary offshoots and the arteries that provide blood to the limbs. The range of clinical manifestations associated with PAD encompasses individuals with symptomless conditions, those who undergo intermittent claudication (IC), and those exhibiting more serious signs of critical limb ischemia. PAD is a common condition that affects a large proportion of the adult population worldwide. The condition occurs predominantly in individuals between the ages of 45 and 70 years and present much more frequently in males than in females [1]. The estimated prevalence of claudication ranges from 0.4% to 14.4%. The occurrence of symptomless conditions identified through noninvasive examinations is notably greater, varying from 0.9% to 22%. The proportion of symptomatic cases to symptomless cases ranges from 1:0.9 to 1:6.

Factors that elevate the risk of atherosclerosis, such as advancing age, smoking, diabetes, dyslipidemia, and hypertension, enhance the probability of developing PAD in the lower extremities [2]. Individuals often report experiencing limb pain consistent with intermittent claudication, along with walking difficulties. Eventually, they may also encounter rest pain, notably at night, which can be described as sensations of coldness, burning, heightened sensitivity, and tingling [3].

Low-level laser therapy (LLLT) is a promising non-invasive physiotherapeutic method. The primary objective of this research was to investigate the impact of low-level laser therapy on the blood circulation to the lower extremities.

Material and Methods
Thirty-six (n=36) individuals treated in Warsaw Outpatient Clinics of Vascular Surgery were qualified for the study. All individuals had symptoms of intermittent claudication. The claudication distance was not less than 200 meters (Fontaine's stages II B). Segmental or total occlusion of the superficial femoral artery was found in ultrasound examination in all individuals. The duration of symptoms ranged from 6 to 27 months. All individuals had pharmacological therapy in accordance with the TASC II guidelines and walking training (3 times a week from 3-6 kilometers). All individuals underwent a Doppler ultrasound examination of the popliteal artery with flow measured in cm/sec performed once a week for 12 weeks. Each individuals received an application with Erchonia EVRL device, which emits a red laser (635 nm) and blue/violet laser (405 nm) both at 7.5mW. The laser procedure was performed once a week for 15 minutes. The area on the thigh was irradiated to the height of the occluded artery. Each individual provided written informed consent prior to participating in any study-related activity.

Results
All thirty-six (n=36) individuals completed the study. The age ranges from 41–80 years, with 24 men (67%) and 12 women. Among the respondents, there were 21 finger smokers, which constituted 58% of the study group and 15 people with diabetes, which constituted 42% of the study group. 10 subjects (28%) were both smokers and had diabetes.

Gender: n (%)		Smoking: n (%)		Diabetes: n (%)	
Male	24 (67%)	Smoker	21 (58%)	Diabetic	15 (42%)
Female	12 (33%)	Non-Smoker	15 (42%)	Non-Diabetic	21 (58%)

Change in Flow Measurement (cm/sec): (Baseline) to 12 Weeks (Endpoint)

The data presented in Table 1 displays the average, standard deviation, and range of flow measurements (expressed in cm/sec) for all participants, both at the initial Baseline and at the 12-week mark (Endpoint), along with the observed change between these two measurements.

Table 1: Flow Measurement (cm/sec): Baseline to 12 Weeks.

	Baseline	12 Weeks	Change
Mean	32.86	79.31	46.44
Std. Dev.	4.65	7.93	7.88
Range	21 - 39	67 - 93	31 - 64

A t-test for two correlated samples was performed to evaluate the significance of the change in mean flow measurements from baseline to week 12 evaluation, and it was found that the mean 46.44 cm/sec change in flow measurement was statistically significant at $p<0.0001$ ($t=-35.38$, $df=35$).

Change in Flow Measurement (cm/sec): Across All Assessments

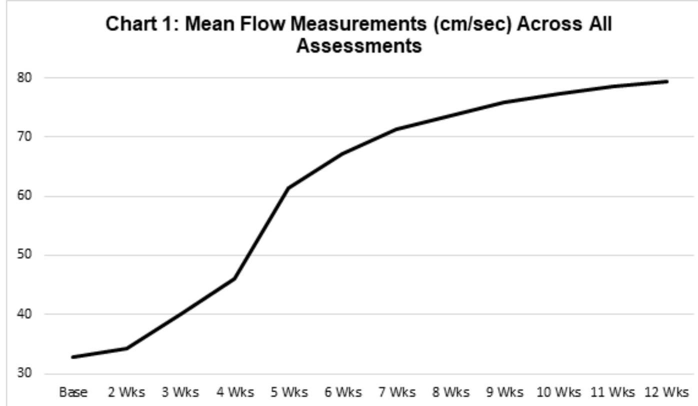
The data presented in Table 2 demonstrates the mean, and standard deviation of flow measurements (cm/sec) across all subjects as measured at each weekly assessment point.

Table 2: Flow Measurement (cm/sec): All Assessment Points.

	Baseline	2 Weeks	3 Weeks	4 Weeks	5 Weeks	6 Weeks
Mean	32.86	34.22	40.11	46.08	61.36	67.25
Std. Dev.	4.65	5.01	4.80	4.28	7.20	6.95
	7 Weeks	**8 Weeks**	**9 Weeks**	**10 Weeks**	**11 Weeks**	**12 Weeks**
Mean	71.31	73.64	75.94	77.31	78.61	79.31
Std. Dev.	7.09	7.76	8.05	7.54	7.56	7.93

Chart 1 shows the trajectory of the mean flow measurements (cm/sec) across the 12 weeks of the study according to the values listed in Table 2 above.

A One-Way ANOVA for 12 correlated samples was performed to evaluate the significance of the changes in mean flow measurement across study duration, which was found to be statistically significant, at $p<0.0001$ ($F=235.159$). This indicates that the consistently progressive increases in mean flow measurement that occurred across study progression is statistically significant.



Flow Measurement (cm/sec): Baseline to 12 Weeks: Analysis by Gender

Table 3 below shows the mean, standard deviation, and range of mean flow measurements (cm/sec) as measured at baseline and at 12 Weeks, and the change between the two values, by gender.

Table 3: Flow Measurement (cm/sec): Baseline to 12 Weeks: Gender Analysis.

	Male (n=24)			Female (n=12)		
	Baseline	**12 Weeks**	**Change**	**Baseline**	**12 Weeks**	**Change**
Mean	33.21	79.13	45.92	32.17	79.67	47.50
Std. Dev.	4.27	8.56	7.15	5.46	6.84	9.41
Range	26 - 39	67 - 93	35 - 58	21 - 39	70 - 92	31 - 64

The difference in t he change i n mean flow measurement from baseline to 12 Weeks between male and female subjects is 1.58 cm/sec, in favor of female subjects. A t-test for two independent samples found this difference to b e not statistically significant, at $p>0.05$ ($t=+0.56$, $df=34$, $p=0.58$). Therefore, gender did not influence the treatment effect of the red/violet laser on flow measurement in individuals with ischemia of the lower limbs.

Flow Measurements (cm/sec): Baseline to 12 Weeks: Analysis by Diabetic Status

Table 4 below shows the mean, standard deviation, and range of mean flow measurements (cm/sec) as measured at 1 Week and at 12 Weeks, and the change between the two values, by diabetic status.

Table 4: ow Measurements (cm/sec): 1 Week to 12 Weeks: Diabetic Status.

	Diabetic (n=15)			Non-Diabetic (n=21)		
	Baseline	**12 Weeks**	**Change**	**Baseline**	**12 Weeks**	**Change**
Mean	32.40	73.20	40.80	33.19	83.67	50.48
Std. Dev.	3.91	3.45	3.53	5.18	7.34	7.67
Range	26 - 39	69 - 80	36 - 47	21 - 39	67 - 93	31 - 64

The mean change in flow measurements from baseline to 12 Weeks assessment is 9.68 cm/sec, in favor of subjects who do not have diabetes. A t-test for two independent samples found this difference to be statistically significant, at $p<0.0001$ ($t=-4.54$, $df=34$). Therefore, diabetic status did influence the treatment effect of the red/violet laser with respect to changes in flow measurement in individuals with ischemia of the lower limbs, with individuals who did not have diabetes evidencing statistically significant greater increases in flow measurements than individuals who had diabetes, to the effect of 9.68 cm/sec.

Flow Measurements (cm/sec): Baseline to 12 Weeks: Analysis by Smoking Status

Table 5 below shows the mean, standard deviation, and range of mean flow measurements (cm/sec) as measured at 1 Week and at 12 Weeks, and the change between the two values, by smoking status.

Table 5: Flow Measurements (cm/sec) 1 Week to 12 Weeks: Smoking Status.

	Smoker (n=21)			Non-Smoker (n=15)		
	Baseline	12 Weeks	Change	Baseline	12 Weeks	Change
Mean	31.29	76.05	44.76	35.07	83.87	48.80
Std. Dev.	4.95	6.73	8.29	3.17	7.37	6.83
Range	26 - 39	67 - 93	31 - 60	28 - 39	72 - 92	40 - 64

The mean change in flow measurements from baseline to 12 Weeks is 4.04 cm/sec, in favor of subjects who are non-smokers. A t-test for two independent samples found this difference to be not statistically significant, at $p>0.05$ ($t=-1.55$, $df=34$, $p=0.13$). Therefore, smoking status did not influence the treatment effect of the red/violet laser on flow measurement in individuals with ischemia of the lower limbs.

Discussion

The peak systolic velocity (PSV) within the popliteal artery can differ based on elements like age, overall well-being, and individual distinctions. Nonetheless, as a general reference point, the usual peak PSV is 60-80 cm/sec in popliteal arteries [5]. Concerning PAD, this condition entails the constriction or closure of arteries, resulting in diminished blood circulation to the limbs. Individuals in this study had a mean PSV measuring 32.86 cm/sec signifying a noteworthy blockage within the artery. However, by the conclusion of the study, the average flow velocity had increased to 79.31 cm/sec, falling within the typical range of values considered normal PSV, signifying a healthy blood flow within the popliteal artery. The outcomes demonstrated continuous and gradual rise in mean flow measurements throughout the study's progression. Notably, individuals without diabetes demonstrated statistically significant higher enhancements in flow measurements compared to individuals with diabetes, while gender or smoking status did not affect the treatment of the red/violet laser on flow measurement in lower limb ischemia individuals.

The influence of red LLLT on vascular health has been substantiated by its effects on vascular endothelial growth factor (VEGF) [6,7]. It is believed that VEGF is responsible for the initial stages of angiogenesis, regulating and stimulating the initiation of this process [8]. In one study, the effects of red LLLT were examined on human umbilical vein endothelial cells [9]. Exposure to low-level laser radiation with a wavelength of 630nm and a power of 30 mW resulted in a 30% rise in VEGF gene expression within vascular endothelial cells, compared to the control cells that were not subjected to laser irradiation. While the application of laser radiation with a wavelength of 808 nm also led to an increased expression of the VEGF-A gene, the differences were not statistically significant in comparison to the control group. Hypoxia, defined as an insufficiency in oxygen supply to tissues, holds a significant role in the context of PAD. The accumulation of arterial plaque due to atherosclerosis restricts the blood flow towards peripheral tissues [10], consequently, the capacity of the blood to carry oxygen to these tissues diminishes. This reduced blood flow leaves a scarcity of oxygen accessible for cellular metabolism, potentially prompting the onset of hypoxia. A previous investigation assessed the impact of LLLT on endothelial cells under conditions of normal oxygen levels (normoxia) and reduced oxygen levels (hypoxia), in the presence and absence of red (650 nm) and near-infrared (808 nm) laser diode irradiation [11]. It was uncovered that light-induced angiogenesis occurred more effectively in the response from 650 nm light in comparison to 808 nm light. The enhanced response was partly attributed to the activation of VEGF production by macrophages, which was observed alongside an elevation in the count of M2 macrophages following light exposure under hypoxia conditions.

Although there has been limited exploration into the effects of violet/blue laser on vascular health, we posit that the outcomes of our study could be associated with the impact of violet light on nitric oxide (NO) production. NO is a signaling molecule generated by endothelial cells lining the inner surfaces of blood vessels. In individuals with PAD, the blood vessels within the affected limbs might be narrowed or constricted due to the presence of atherosclerosis (the accumulation of plaque inside arteries). NO counteracts this constriction by inducing the dilation of blood vessels, thereby augmenting blood flow to the affected region. This vasodilation enhances the delivery of oxygen and nutrients to muscles and tissues, thereby alleviating symptoms such as pain and cramps often associated with PAD [12]. Pope et al., conducted a study measuring alterations in intracellular NO levels based on variations in laser wavelength and irradiance [13]. Alterations were observed in intracellular NO levels that were dependent on the specific wavelength of laser exposure. Among single wavelength exposures, it was noted that exposure to 447nm triggered the most substantial increase in NO levels. Specifically, the impact of the 447-nm blue exposure stood out with a remarkable 33.6% increase ($p < 0.001$ when compared to red, blue, and near-infrared wavelengths). Drawing from the historical data on LLLT, our conviction is that LLLT expedites the generation of blood vessels and connections within collateral circulation. This notably influences the restoration of regular blood flow to the popliteal artery.

Conclusion

Our results indicate the therapeutic potency of red and violet LLLT in the treatment of PAD. Laser therapy is equally effective for women and men, and smoking did not have a statistically significant effect on the progression of neo angiogenesis. Further confirmation of the efficacy of low-level laser therapy as a frontline therapy for peripheral vascular diseases necessitates a future multicenter study expansion.

Conflicts of Interest

Dr. Andrzej Eberhardt performed all duties in this case series (including laser procedures, doppler ultrasound and data capturing) at his respective independent site. Dr. Eberhardt received no financial support for the research and has no conflict of interest. Travis Sammons is an employee of manufacturer of the EVRL device (Erchonia Corporation) and co-authored the manuscript.

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